Viewpoint: Policy Requirements for Protecting Wildlife from Endocrine Disruptors

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Man-made endocrine-disrupting chemicals (EDCs) present a threat to biodiversity, even in remote areas. To date, numerous wildlife species have been affected by EDCs in the environment, but it is likely that many more species are suffering effects that have not yet been reported. Impaired reproduction, damaged brain function, and deficits of the immune system are of particular concern. In order to bring all endocrine-disrupting chemicals under control, the development of screens and tests to identify EDCs must be expedited. However, the World Wildlife Fund (WWF) considers that sufficient information is already available to merit action on several such substances. In addition, it must be recognized that proving the mechanism of action for some chemicals may take decades. Therefore, it is important to enable certain chemicals to be brought under stricter control on the basis of strong suspicion of endocrine disruption or biochemical signaling disruption. Furthermore, the risk assessment process itself also must be modified, and some suggestions are discussed in this article. WWF maintains that any effect that could reasonably be expected to affect the population level should be taken forward in environmental risk characterization, in particular, behavioral effects should be given more consideration. Current chemical management policies are not protective, and we argue for modifications in them to be made. *Key words:* chemical definition, EDCs, endocrine disruptors, environment, hormone, legislation, pollution, risk assessment, species. *Environ Health Perspect* 114(suppl 1):142–146 (2006). doi:10.1289/ehp.8070 available via *http://dx.doi.org/* [Online 21 October 2005]

In a world in which wildlife populations are increasingly threatened by climate change and biodiversity has already declined at an alarming rate because of habitat destruction, the potential effects of chemical-induced endocrine disruption in wildlife might seem to pale into insignificance. However, man-made chemical pollution is widespread, and even remote environments formerly considered to be pristine are now contaminated. From sea birds in Antarctica to polar bears in the Arctic (Giesy and Kannan 2001; Martin 2002; Priddle 2002; Sandau et al. 2000), most, if not all, species are exposed to some extent, and effects have already been reported in many locations. Female mollusks growing penises (Bryan et al. 1986), intersex in fish (Jobling et al. 1998), altered parenting behavior in birds (Kubiak et al. 1989; McCarty and Secord 1999), and impaired reproduction and immune system dysfunction in mammals (Bergman 1999; Lie et al. 2004) are just some of the alarming observations in wildlife that have been attributed to chemical contaminants.

Controlled experiments confirm the role of pollutants in causing deficits in immune system function (de Swart et al. 1994). Other studies highlight the vast array of effects that chemicals with endocrine-disrupting properties can cause in animals. Particularly noteworthy are the effects on reproduction and related behavior (Gray et al. 1999a; Lee and Veeramachaneni 2005; Veeramachaneni et al. 2001), and the malformations of the male reproductive tract that have been reported (Gray et al. 1999b).

High levels of persistent organic pollutants are found in the Arctic because pollutants are carried on air and ocean currents by a process termed "global redistillation." There, many species (including peregrine falcons, bald eagles, white-tailed sea eagles, glaucous and great black-backed gulls, great skuas, some alcids, harbor porpoise, seals, Steller sea lions, belugas, long-finned pilot whales, narwhal, minke whales, killer whalers, sea otters, polar bears, and Arctic fox) have tissues with total dichlorophenyltrichloroethane (DDT) and related breakdown products, total polychlorinated biphenyls (PCBs), and/or dioxin-like substances at levels that exceed those at which reproductive and/or immunosuppressive effects are expected based on extrapolation from known thresholds for such effects in other animals [Arctic Moninotiring and Assessment Programme (AMAP) 2004].

Similarly, in the remote North Pacific Ocean, researchers have concluded that the toxic equivalent concentrations (TEQs) based on the levels of polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans, and coplanar PCBs in black-footed and Laysan albatrosses are high enough to be suspected of causing adverse effects (Tanabe et al. 2004).

In view of such findings and the extent of global contamination, WWF considers that chemicals pose a very real threat to species conservation and to some of the world's most precious remaining wildernesses.

Inherent Problematic Properties of Endocrine-Disrupting Chemicals and Delayed Effects

Endocrine-disrupting contaminants pose an insidious threat because exposure in early life during development can lead to subtle irreversible organizational effects that may be masked until the offspring reach maturity. Some chemicals with endocrine-disrupting properties may also cause transgenerational effects (effects carried across generations as a consequence of events that happen during the lifetime of the previous generation). For example, in laboratory experiments, nonylphenol caused poor survival in the subsequent generation of the Pacific oyster, *Crassostrea gigas* (Nice et al. 2003), and octylphenol caused developmental abnormalities in the subsequent generation of Japanese medaka, *Oryzias latipes* (Gray et al. 1999c). Similarly, rodent experiments with the drug diethylstilbestrol (DES) illustrate that an increased susceptibility for tumors is transmitted from the DES "grandmothers" to subsequent generations. For example, when DES was administered to pregnant mice, not only their offspring but also their "granddaughters" (Newbold et al. 1998) and "grandsons" (Newbold et al. 2000) had higher rates of certain tumors. Such transgenerational effects may occur in humans. For example, a study of boys born to women exposed to DES *in utero* suggested that there is an increase in hypospadias (Klip et al. 2002).

If an endocrine-disrupting chemical (EDC) has the ability to bioaccumulate, then female adults may detrimentally pass on some of their body burden to their offspring during critical developmental periods while the young are in the womb or in the egg, despite the fact that the adult's intake of the chemical may no longer be current. Moreover, because the female ova are formed at the fetal stage and environmental contaminants have been found in follicular fluid, it may be that offspring can be affected directly by their grandmother's exposure. Delayed effects may also arise for a number of other reasons, not the least of which because it may take some time for persistent chemicals to reach levels of concern or to be transported in the environment to the organism or ecosystem where they exert their

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effect. This delay means that for some species, future effects may be inescapable.

Difficulties in Observing Endocrine Disruptors Damage in Wildlife

Effects caused by endocrine disruption are even now likely to be passing unnoticed because only a very small fraction of the many wildlife species on the planet have been investigated. Even in prominent species such as fish, endocrine disruption effects may be being missed. The abnormal production of the egg yolk protein vitellogenin in male fish has now been found in several countries (Damstra et al. 2002), but was probably going on for many years before its detection in several polluted U.K. rivers (Harries et al. 1996). Furthermore, studies are complicated because effects may be different even in closely related species. For example, vitellogenin production was not found in male sand gobies from estrogen-contaminated estuaries in the United Kingdom, but instead they exhibited deformed and feminized urogenital papillae, which is the structure used by both sexes to deposit gametes (Matthiessen et al. 2002).

Behavioral effects in the wild may be missed even more easily than structural effects. However, behavior provides a sensitive integrated end point of many complex processes, and in wildlife, altered behavior may detrimentally affect survival. Even small deficits in brain function could render the animal less able to escape predation, catch prey, find a mate, and rear offspring. Environmental exposure routes can be instrumental in affecting behavior. This is exemplified by a controlled experiment showing that the pollutants present in sewage sludge affect the emotional reactivity and exploratory behavior of lambs (Erhardt and Rhind 2004). Unfortunately, in the Arctic, PCBs have now reached such high levels that in some representatives of numerous mammalian species (including polar bears, Arctic fox, reindeer, mountain hares, wolverines, walrus, grey whales, seals, Steller sea lions, harbor porpoise, walrus, minke whale, killer whales and narwhal) they exceed those levels that have been associated with subtle neurobehavioral effects in the offspring of rhesus monkeys and humans (AMAP 2004). However, despite that PCBs can alter thyroid hormone levels, it is still not clear whether these neurobehavioral effects are mediated by endocrine disruption.

Sex hormone disruption may particularly affect breeding behavior. To mate with a female, a male may have to display courtship behavior, build a nest, and chase or show some dominance. Even if the concentrations of endocrine-disrupting compounds in the environment are not sufficient to cause structural effects and reverse sexual physiology, small adjustments in behaviors could still be devastating to reproductive success. In wild birds, manmade chemicals have already been associated with altered pairing and impaired parenting behavior (Fox et al. 1978; Hunt and Hunt 1977; Kubiak et al. 1989; McCarty and Secord 1999). Laboratory studies highlight well-founded concerns. For example, developmental exposures to mixtures of common industrial pollutants or to vinclozolin, an antiandrogenic sex hormone–disrupting fungicide, can affect the sexual behavior and erectile function of rabbits such that some males exposed to the mixture prefer male teasers to achieve erection and ejaculation (Veeramachaneni et al. 2001) or they show no sexual interest in mounting females or males (Veeramachaneni 2000, 2004, 2006). In fish, Bell (2001) found that the courtship and territorial behavior of the male stickleback fish (*Gasterosteus aculeatus*) is affected at the levels of ethinylestradiol found in some rivers.

Indirect effects on wildlife populations should also be considered. For example, Kiesecker (2002) found that EDCs may reduce the resistance of amphibians to parasitic diseases. Similarly, organochlorines in the Arctic have been associated with deficits in the functioning of the immune system in polar bears (Lie et al. 2004). Immune suppression is also believed to have played a role in the devastating mass dieoffs of seals with viral infections (Hall et al. 1992). However, it is still not clear whether these reported examples of immune system suppression are mediated by endocrine disruption. Nevertheless, the immune system is known to communicate and cooperate with the neuroendocrine system (Damstra et al. 2002), such that some investigators consider the immune system to be a subpart of the endocrine system (T Colborn, personal communication, 2004).

Disruption of the adrenocorticoid system could also lead to increased susceptibility to environmental stressors such as severe weather or predatory or human disturbance. For example, Love et al. (2003) reported impaired cortisone stress response in captive kestrels exposed to an environmentally relevant level of PCBs. Moreover, fish studies show that chronic exposure to a wide range of contaminants can inhibit normal stress responses (Pottinger 2003).

Widespread Vulnerability to EDCs

Most species are vulnerable to EDCs because the endocrine system has been conserved during evolution and, therefore, has many similarities in all vertebrates, and in some invertebrates. Therefore, it is likely that endocrine disruption is more widespread than has been currently reported. Already, a review by Miyamoto and Burger (2003) has noted that over 200 species are either known or suspected to have been affected by endocrine-disrupting substances, including examples from all five major vertebrate classes, and from at least two invertebrate phyla.

Research Needs

Research is needed to identify sensitive species that can be used as sentinel species in the wild. The research conducted on amphibians by Hayes et al. (2003) also points to the need to ensure that species in decline are fully investigated as to the potential effects of pollutants, including endocrine disruptors. Ecologically important species should also be prioritized for indepth further research. For example, bees are important pollinators of crops and wild flowers, and research into the impact of the insecticides diflubenzuron and fenoxycarb on honeybees has demonstrated that nonpersistent compounds that interfere with insect hormone systems can have long-term effects on these social insects (Environmental Data Services Ltd 2004). However, current registration approval schemes for pesticides do not pay sufficient attention to the long-term effects on nontarget species, and there could be significant effects on species such as bumblebees that reproduce slowly, several of which are already endangered.

Resource Needs for Test Methods

Responsible parties, particularly corporations, should provide more resources to develop the much-needed screens and tests to identify chemicals that can disrupt the hormone system. Although some research is under way, much still needs to be done. *In vitro* receptor binding assays for estrogen and androgen disruptors have been developed, but these tests can miss some *in vivo* activity. For example, these assays would not detect chemicals that interfere with steroid biosynthesis and metabolism, such as those that disrupt important steroidogenic enzymes like 5α-reductase and aromatase. Also, given the importance of the brain in guiding all species through life, more research is needed into thyroid hormone disruption and into the mechanisms of developmental neurotoxicity. Important subtle behavioral effects need to be identified and investigated, and new test methods must be developed, as many such effects would not be picked up in current testing programs. More research is also needed into chemical disruption of the adrenal glands and corticosteroid hormone disruption, with effort focused on laying the foundations for test methods development. Furthermore, robust nonvertebrate animal test methods must be developd because such techniques tend to be quicker and cheaper and are more publicly acceptable.

Nevertheless, the current lack of test methods to identify all chemicals that may have hormone-disrupting properties should not be an excuse for regulatory inaction. Some currently available test methods are sufficient to raise concern regarding the potential endocrine-disrupting properties of some substances.

Meetings of the Organisation for Economic Co-operation and Development Task Force on Endocrine Disrupters Testing and Assessment are instrumental in deciding which test methods should be prioritized for development and international validation and harmonization. Such decisions should be based on scientific deliberations involving independent scientists, and moreover should be informed by prior discussions as to which tests are considered most important for use in legislative frameworks in the participating countries. To promote more input from independent scientists, we need resources or research credits for academic scientists who devote time to these activities.

Policy Needs for Securing Adequate Controls over EDCs

In 1997 the international "Endocrine Disrupter Workshop" on EDCs was held 23–24 January 1997 in Washington, DC. This workshop was a collaborative effort of the Smithsonian Institution, the United Nations Environment Programme, the White House Office of Science and Technology Policy, and the U.S. Environmental Protection Agency. At this meeting, delegates considered whether EDCs should be the focus of global coordinated action, including legislative action. However, they acknowledged that a prerequisite to any further consideration would be a written global assessment of the state of the science. This document was therefore commissioned and subsequently published by the World Health Organization (Damstra et al. 2002), with the following definition for EDCs:

> An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.

However, WWF is concerned about this definition being used in legislation, as it could result unnecessarily in long delays in confirming which chemicals fall within the scope of the definition. If a substance were required to meet this definition before it could be subject to certain legislative controls, the observed effect would have to be proved a consequence of the endocrine disruption. It would not be enough for a chemical to be shown to alter hormone levels or for an impact to be causally linked to that chemical. Unless the mechanism of action was established beyond doubt to be mediated by the endocrine system (rather than the changes in the endocrine system being a consequence of another mechanism of toxicity), the chemical would not be eligible to be judged an endocrine disruptor. Yet even for a well-studied effect such as eggshell thinning caused by DDT, it is not known with certainty whether this thinning is mediated by endocrine disruption. Similarly, as exemplified by cigarettes and lung cancer, it may take decades for a causal mechanism(s) to be identified. Therefore, it is important that the strict control of such substances not depend on the absolute certainty as to the causal mechanism.

WWF considers that, particularly for legislative purposes, the term "EDC" should not be overly restricted. Hormones do not work alone; rather, they require auxiliary systems, including enzymes, neurotransmitters, growth factors, and other proteins, which WWF suggests should all be considered as much a part of the endocrine system as the hormones themselves. The salient point about EDCs is that they hijack biochemical messenger systems, often by mimicking or blocking the action of the bodies' own chemical messengers, so that even small doses at the wrong time may cause subtle but important alterations. It is disruption of the bodies' internal signaling mechanisms during development that is really the issue, and, as such, perhaps the term "EDCs" should be broadened to include "signaling or system disruptors."

The European Commission is now trying to press ahead on the legislative front and is proposing in its REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulation to enable EDCs to be brought under strict controls so that their usage could require prior authorization [European Commission (EC) 2003]. Moreover, the granting of an authorization for use would be subject to certain stringent conditions. Hopefully, the EU REACH legislation has obviated the need for an agreed definition as such, or proof of the causal mechanism, by proposing that "substances, such as those having endocrine disrupting properties . . ." could be subjected to the prior authorization requirement. However, as of 2005 the negotiations on REACH were not yet finalized.

Several other issues need to be addressed to secure adequate controls over EDCs. First, many chemicals are not tested at low dose levels or at the most sensitive exposure period. And even if they were, it may be that the statistical power of such laboratory tests is simply not adequate to pick up effects that occur in a small proportion of the exposed organisms. The concern is that because EDCs act on a biochemical system that is already active, it may be that for some chemicals there is no threshold for certain effects.

Second, the assessment factors used in the risk assessment may be inadequate, particularly considering all species may be vulnerable to hormone disruption. For example, in the EU risk assessment process, laboratory tests are used to find the predicted no effect concentration, or safe level. In this process, "assessment factors" of 1,000, 100, or 10 are typically used to extrapolate from the test species to the world at large, depending on whether data for several test species are available. However, it is clear that for chemicals with certain modes of action, these "assessment factors" are often inadequate, as species sensitivity distributions can cover from 2 to > 5 orders of magnitude (Escher and Hermens 2002). For endocrine disruptors, for example, work by Oehlmann and colleagues (2006) has shown that some mollusk species are far more sensitive to bisphenol A than the typically tested organisms.

Third, the risk assessment process does not consider the fact that in the wild, there is exposure to many chemicals with potentially additive effects. The effects of other stressors also need to be considered because many factors will make animals in the wild more vulnerable to these stressors than those in the laboratory.

Fourth, the interpretation of when an effect can be termed "adverse" needs to be less restrictive, or there is a danger that legislation will be used only to control chemicals already known to be harmful in the wild rather than to try to prevent harm. Unlike human risk assessment, where the aim is to protect every person, in environmental risk assessment, the aim is to protect only the population level. However, WWF considers that ecological risk assessment should move away from regulating chemicals on the basis of the concentration for which there is good evidence for predicting population-level effects and move toward protecting the individual organism. This change should come about because current risk assessment methodology presents too much regulatory difficulty to prove that certain effects will ultimately lead to a reduction in the population level. Unfortunately, the distinctions made between findings that are likely to affect the population level and those that are not may be unrealistic and somewhat artificial, as there is no accepted way of reliably distinguishing between them in laboratory tests. For example, effects on spermatogenesis in fish may not affect the population level in the laboratory, but this outcome may not hold true in the wild where males have to compete for females, and the conditions are generally less optimal. Even small deficits in sperm production in the wild might lead to population-level effects that would not be apparent in the laboratory. Currently, there is a lack of data on the effects of EDCs on the genetics of fish populations. However, fewer males contributing to the next generation would be a concern because it is generally believed by conservationists that a considerable proportion of breeding individuals is necessary if a genetically viable population is to be sustainable [Institute for Environment and Health (IEH) 2004].

In the EU, the significance of other effects has also been a matter of debate. For example, Kwak et al (2001) exposed swordtail fish (*Xiphophorus helleri*) to bisphenol A and observed a significant reduction in sword length. The draft Risk Assessment Report (EC 2003) stated the following:

> significance of the changes in sword length is not understood. It is thought that the length of the sword has an influence on mating success, with female fish preferring males with longer swords, but it is not clear what degree of change should be considered to be significant.

However, WWF argues that any alteration in a secondary sexual characteristic is likely to affect the female's choice of breeding partner and is likely linked to a survival strategy so that altered pairing might make the population less able to cope with other stresses. Similarly, WWF argues that behavioral effects observed in test systems, such as altered exploratory behavior, should also be considered adverse and likely to affect a population. Guidance is certainly needed on the types of behavioral data that should be collected during laboratory or field studies and how they should be interpreted in the risk assessment. To summarize, WWF suggests that ecological risk assessment should move toward protection of the individual rather than just the population level and that even subtle changes should be considered adverse. Effects should certainly be considered adverse if they could reasonably be conjectured to give rise to a population-level effect. The complexities of ecosystems and the numerous threats and stressors they face are such that the environment should be given the benefit of any doubt. Such a cautious approach is necessary because if the population level of just one species is directly adversely affected, this effect may then have unforeseen consequences for many other species. In line with such an approach, some delegates at a recent round table meeting convened by the U.K. Department of the Environment Food and Rural Affairs also supported regulatory action on EDCs if significant effects were seen in individual animals, even if the impact on populations was unknown or uncertain (IEH 2004).

Finally, there is another issue that has dogged risk assessment, and that is how to decide on the "correct" interpretation when there are contradictory study findings. Over the last decade, numerous studies by independent academic scientists have been strongly criticized or refuted by scientists working for industry. Scientific debate and challenge is needed, but the vested interests of industry need to be recognized as forces that may not always work for the public good (Ong and Glantz 2001). For example, regarding tobacco, Wise (1998) suggested that industry funding can influence results. He showed that review articles written by authors with affiliations to the tobacco industry were 88 times more likely to conclude that passive smoking is not harmful than if the article were written by authors with no connection to the tobacco industry.

To end controversies over conflicting studies and to enable continued objective input into the risk assessment of certain chemicals, funds should be allocated for "blind" duplicate studies in the laboratories of those scientists who have found effects. In addition, there needs to be funding for academic laboratories and laboratories managed by regulatory agencies because studies must be seen to be impartial to ensure confidence in their results. There is also a need to prevent bias in advisory committees.

Conclusion

In conclusion, endocrine disruption is likely to be affecting more than the couple of hundred or so species currently suspected or known to be affected. There is, therefore, a need to ensure continued research into endocrine disruption and to establish pragmatic ways of bringing chemicals of concern under tighter controls. It is essential to improve current regulatory frameworks and to adapt them to current knowledge. Furthermore, to counterbalance the vested interest of industry and to help policymakers consider all aspects, independent scientists should be encouraged to work not only on pure scientific research but also at the science/policy interface.

WWF maintains that to protect biodiversity, we need regulatory frameworks worldwide to prevent the use of chemicals with properties that cause much concern, certainly where safer alternatives exist. Regulation of chemicals should become more protective and precautionary, particularly in the interpretation of what effects should be considered adverse. Unfortunately, current legislation is such that pollution control has largely been a matter of shutting the stable door after the horse has bolted.

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